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MINERAL SUPPLEMENTS: ARE THEY REALLY NECESSARY?

OBJECTIVE To analyse the evidence on oral magnesium, selenium and zinc supplementation for the prevention or treatment of health problems. MATERIALS AND METHODS TRIP and PubMed were searched up to August 1st 2018. European Food Safety Authority (EFSA) reports were reviewed. Drug interactions were extracted from UptoDate®. We report the results obtained in recent studies and systematic reviews assessing the efficacy of oral mineral supplementation. RESULTS AND CONCLUSIONS Magnesium supplementation reduces blood pressure, although reductions are not clinically relevant. Zinc in combination with other antioxidants may reduce the risk of age-related macular degeneration (AMD) progression. Although this effect has been consistently demonstrated in several studies, more research is needed to determine the dose and duration of zinc supplementation. Selenium supplementation does not provide any benefit. Selenium deficiency can be prevented by an adequate dietary intake.
KEYWORDS Magnesium, selenium, zinc, oral supplements, diet, mineral supplements.

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Introduction

Minerals –which are necessary for maintaining homeostasis– are classified into three groups according to their recommended daily intake: macroelements (sodium, potassium, chlorine, calcium, phosphorus, magnesium), microelements (iron, zinc, copper, manganese, fluorine) and trace elements (arsenic, boron, chromium, iodine, selenium, silicon, nickel, vanadium).[1]

The belief that some health problems could be treated or prevented with mineral supplementation and that supplements are healthy or can make up for unhealthy habits have resulted in an increase in the consumption of mineral supplements, be it under medical prescription or not.[2]

The effects of magnesium, selenium and zinc supplementation on health were selected, because they are common oral mineral supplements available in the market. A literature search was performed on PubMed, TRIP database and UpToDate® up to August 1st 2018 to examine the evidence available on the clinical benefits of oral magnesium, selenium and zinc supplementation.

Identifying the specific effects of each mineral on health is challenging, as they are generally ingested in combination with other minerals.

Table 1 shows recommended daily allowances (DRVs) for each mineral by age and sex.

Magnesium

Magnesium (Mg) is an essential element mainly found in bones, muscles and soft tissues. Its functions include muscle contraction and coagulation in combination with calcium.[6]

Ionized magnesium is absorbed in the distal portion of the small intestine. Absorption is improved by fermentation of the soluble fibre. Mg is an important component of unprocessed foods. However, the spread of the Western diet characterised by high intakes of sugar, animal fat, carbohydrates, meats, and refined grains has contributed to a reduction in the dietary intake of Mg. According to EFSA,[4] the recommended daily intake for Mg varies with age and sex, as shown in Table 1.

Fertilisers, limited crop rotation and environmental pollution cause soil acidification, which contributes to reduce Mg content in food.[7]

Dietary reference values

The main dietary sources of Mg include nuts, whole grains, whole foods, meat, fish, seafood, vegetables, berries, bananas, coffee and cocoa. Bottled water also contains Mg.[8]

Table 1. EFSA Dietary Reference Values (DRVs) for magnesium, zinc and selenium according to EFSA.[3-5]

Age	Magnesium DRV* (mg/day)	Zinc DRV* (mg/day)	Selenium DRV* (µg/day)
Infants 6 months - < 1 year	80	2 – 2.4	20
Toddlers 1 - < 3 years	170	4.6 – 6.2	17.2-36.3
Children 3 - < 10 years	230	5.5 – 9.3	20.6-45.9
Children and adolescents 10 - < 18 years	250-300	6.8 – 14.5	33.9-60.3
Adults	Men: 350 Women: 300	Men: 9.4 – 16.3 Women: 7.5 – 12.7	Men: 60 Women: 50

*DRV: Dietary Reference Values.

Pregnancy and lactation: There is no evidence that mineral requirements are higher in these situations.

Food	Mg content (mg/ration*)	% DRV**
Chard	122	37
Whole-grain rice	100	31
Chickpeas	85	26
Almonds	77	24
Banana	50	15
Whole-grain bread	49	15
Pasta	42	13
Skimmed milk	40	12
Fish	38	12
Dark chocolate	12	4

(*) Ration: 100 g of edible portion

(**) DRV taken as a reference: 325 mg/day.[9]

Causes and consequences of inappropriate levels in blood

Normal blood Mg levels are (1.7-2.2 mg/dL) which equals (0.85-1.1 mmol/L).

The main causes of Mg deficiency are gastrointestinal disorders (diarrhoea, malabsorption, steatorrhoea, small bowel bypass, acute pancreatitis, treatment with proton pump inhibitors, and intestinal hypomagnesemia with secondary hypocalcemia) and renal losses (treatment with diuretics, antibiotics, calcineurin inhibitors, cisplatin, EGFR inhibitors; primary aldosteronism, uncontrolled diabetes mellitus, alcoholism, hypercalcemia, acquired tubular dysfunction or genetic abnormalities).

The consequences of Mg deficiency include hypocalcemia and hypokalemia, with neurological or cardiac symptoms in severe hypomagnesemia (<1.2 mg/dL or 0.5 mmol / L). Severe hypomagnesemia causes tetany, positive Chvostek and Trouseau signs and seizures. Mg deficiency could also be related to neuromuscular irritability, muscle cramps and tremors, fasciculations, muscle weakness and impairment, restless legs syndrome or fibromyalgia.[4]

Hypermagnesemia is rare, except in cases of renal failure where massive oral intake exceeds renal excretory capacity. This disorder can occur as a result of abuse of magnesium-containing antacids or laxatives. The most common gastrointestinal signs of hypermagnesemia include diarrhoea, nausea and abdominal pain; at muscular level: a decrease in tendon reflexes, weakness, paralysis and lethargy; and at cardiac level: lengthening of the QT interval, hypotension, asystole and respiratory failure.[10]

Lack of regulations facilitates the widespread use of mineral supplements without medical prescription.

Review of the evidence for Mg supplementation

Hypertension and cardiovascular disease

Several studies suggest that Mg supplementation may regulate blood pressure. A meta-analysis of 12 clinical trials (N= 545) involving patients with hypertension revealed that a dose of Mg 243-973 mg/daily taken for 8-26 weeks resulted in a statistically significant reduction in diastolic pressure (2.2 mmHg, 95%CI: -3.4 to 0.9). However, no statistically significant differences were observed in systolic pressure (1.3 mmHg, 95%CI: -4 to 1.5). No severe adverse events were reported in any of the studies.[11]

Another meta-analysis was published of 22 studies (N=1173) in patients with high and normal blood pressure (the 12 studies of the meta-analysis mentioned above were also included). The results showed an average reduction of both systolic and diastolic pressure. Effect sizes were 0.32 (95%CI: 0.27 to 0.44) and 0.36 (95%CI: 0.23 to 0.41), respectively, which corresponded to a true reduction of 3-4 mmHg and 2-3 mmHg, respectively. Mg supplementation consisted of a mean daily dose of 410 mg for a mean of 11.3 weeks (3 to 24 weeks). No adverse events were reported.[12] A meta-analysis of 34 trials (N= 2028) involving patients with high and normal blood pressure (16 and 18 trials, respectively) demonstrated that the administration of 368 mg/daily for 12 weeks reduced systolic pressure by 2.00 mmHg (95%CI: 0.43 to 3.58) and diastolic pressure by 1.78 mmHg (95%CI: 0.73 to 2.82).[13] No adverse events were reported.

The results of these studies show a statistically significant, albeit clinically irrelevant, effect. The National Institute for Health and Care Excellence (NICE) does not recommend Mg supplementation to reduce blood pressure, as reductions are below 5 mmHg.[14]

Type 2 diabetes mellitus

Mg is involved in different pathways of glucose metabolism. Hypomagnesemia could trigger acute-phase reaction and mild inflammatory syndrome, which are related to insulin resistance.[15]

Epidemiological studies have provided evidence that Mg depletion precedes glucose control alterations. Diabetes causes Mg deficiency as a result of urine excretion, which might negatively affect insulin secretion and action, thereby hindering disease control.[16]

Several cohort studies have revealed a significant inverse correlation between dietary Mg intake and the risk of type 2 diabetes.[17] We found a meta-analysis of seven studies on Mg dietary intake alone (n = 4) or in combination with Mg supplementation (n = 3) involving a total of almost 300000 subjects, of whom 11000 had diabetes. All studies except one reported a negative correlation between Mg intake and the risk of diabetes. This relationship was statistically significant in four studies. The RR for every 100mg/day dose increase of Mg was 0.85 (95%CI: 0.79 to 0.92). Similar results were obtained for dietary Mg intake (RR, 0.86; 95%CI: 0.77 to 0.95) and total Mg (RR, 0.83; 95%CI: 0.77 to 0.89).[18]

Apart from the seven studies of this meta-analysis, six other studies were included in another meta-analysis. The results demonstrated a significant negative correlation between Mg intake (either dietary or by supplementation) and the risk of type 2 diabetes (RR 0.78; 95%CI: 0.73 to 0.84). This inverse relationship was significant in patients who were overweight (BMI≥25 kg/m2), but not in subjects with normal weight. Dose response analysis showed a RR of 0.86 for type 2 diabetes for every 100 mg/day dose increase of Mg (95%CI: 0.82 to 0.89).[19]

Further evidence is needed before the intake of Mg can be recommended for patients with type 2 diabetes.

Osteoporosis

Mg is involved in bone formation, as it stimulates osteoblast and osteoclast activity. In addition, Mg affects the parathyroid hormone and the active form of vitamin D, which are involved in the regulation of bone homeostasis. There are few data available that quantify this relationship.

Although the role of Mg in bone structure and physiology is widely known, few studies have been published that determine the strength of this relationship. Therefore, there is no evidence supporting Mg supplementation for osteoporosis treatment.[20]

Migraine

Mg deficiency is related to factors predisposing to migraine: nitric oxide synthesis, serotonin receptor activity, NMDA receptors and other receptors involved in the mechanisms of migraine.[21]

The evidence available suggests that 50% of patients show low levels of Mg in blood and tissues during an episode of migraine.[22] Yet, experience with the use of Mg supplementation in the prevention or reduction of symptoms of migraine is limited. Only a few small studies have been published on this topic. The first study published involved 20 patients and assessed the efficacy of oral Mg supplementation vs. placebo in the prophylaxis of menstrual migraine. The results obtained showed a statistically significant improvement in the two groups after two months of treatment. Pain reduction was greater in the Mg group ($p<0.03$).[23] Another double-blind placebo study in 84 patients with migraine (with and without aura) revealed a 41.6% reduction in the frequency of symptoms associated with the administration of Mg 600 mg/daily orally.[24]

More evidence is needed to determine the relationship between low mineral levels and health problems.

A similar study conducted to determine the efficacy of oral Mg supplementation in reducing the duration or intensity of migraine showed a more substantial reduction in the placebo group as compared to the experimental group (29.4% vs. 28.6%, respectively).[25]

Intravenous Mg has shown to have an analgesic therapeutic gain of 36.7% vs. placebo (defined as the difference between active response rate and placebo response rate) in patients with migraine with aura (NNT 6) one hour after the administration. Positive headache response was a patient's pain changing from moderate or severe pain to mild pain or no pain. In episodes of acute migraine with aura, patients receiving magnesium sulphate presented a statistically significant improvement of pain and of all symptoms compared to controls.[26] Yet, as the evidence available is limited, Mg supplementation is not recommended in clinical practice guidelines for migraine.[27, 28]

Although migraine seems to be related to Mg deficiency, evidence on oral Mg supplementation is scarce.

Depression

At neuronal level, Mg is a calcium antagonist that blocks NMD channels, exerting a neuroprotective effect and preventing cell death. Studies in animals suggest a possible antidepressant and anxiolytic effect.[29]

No conclusive evidence has yet been provided on the relationship between serum Mg levels and symptoms of depression. Some studies show a positive correlation,[30] while others demonstrate a negative correlation[31] or no correlation at all.[32] A prospective study was performed

in almost 13000 Spanish university students without depression to determine the relationship between Mg intake and depression. The results suggested that a higher Mg intake was not related to a lower risk for depression.[33]

Pregnancy

In a Cochrane review including 10 trials, 9090 participants were randomised to receive either oral Mg or placebo/no intervention. There was wide variability in the dose, composition and duration of Mg supplementation across studies. No statistically significant effects were found in perinatal mortality, pre-eclampsia and premature birth. The available evidence is insufficient to supports the recommendation of Mg supplementation during pregnancy.[34, 35]

Drug interactions

Bisphosphonates
Mg supplementation reduces the absorption of oral bisphosphonates. Therefore, Mg should be taken 30 min. to 2 hours after bisphosphonate.[36]

Antibiotics
Some oral antibiotics such as tetracyclines or quinolones taken concomitantly with Mg salts generate the formation of insoluble complexes in the gastrointestinal tract, thereby blocking absorption. Mg should be ingested at least two hours before or 4-6 hours after antibiotics.[36]

Integrase inhibitors
Absorption of integrase inhibitors (raltegravir, dolutegravir, elvitegravir) can be reduced by the formation of a polyvalent ion binding complex. Thus, it is recommended to take Mg at least 6 hours before or 2 hours. after integrase inhibitors.[37]

Diuretics
Chronic therapy with loop and thiazide diuretics can increase Mg urine excretion, however potassium sparing diuretics reduce its excretion.[38]

Mycophenolate
Concomitant administration of mycophenolate and Mg reduces mycophenolate concentrations; therefore, it is recommended that they are taken apart.[36]

Eltrombopag
Concomitant administration can reduce serum eltrombopag levels. It is recommended that it is ingested 2 hours before or 4 hours after oral Mg.[36]

No conclusive evidence has demonstrated the efficacy of mineral supplementation in disease prevention.

Contraindications

Hypersensitivity or known allergy to any of the components of Mg supplements, severe kidney failure due to risk of hypermagnesemia, heart block, ischemic heart disease, arrhythmias, diabetic coma, myasthenia gravis, chronic diarrhoea, ulcerative colitis, ileostomy, symptoms of appendicitis.[39]

Mg supplements available on the Spanish market

Some magnesium-containing compounds are available on the market:

Pharmaceutical forms available on the Spanish markets (Spain)	Magnesium (Mg)
Actimag® Solution	87 mg/g
Elevit® film-coated tablets	100 mg/tablet
Hidropolivit "a" mineral® chewable tablets	6 mg/tablet
Magnesioboi® 48,62 mg tablets	48,62 mg/tablet
Magnesium Pyre® 64 mg tablets	64 mg/tablet
Magnogene® 53 mg coated tablets	53 mg/tablet

* Data extracted from BOTPLUS®[40]

Zinc

Zinc (Zn) is an essential trace element that is necessary for numerous metabolic and physiologic activities including growth, immune mechanisms, reproduction and neurological development.[41, 42] Zinc intake is closely related to protein intake. During digestion, dietary zinc is released and primarily absorbed by the duodenum and jejunum and, to a lesser extent, by the ileum and the large intestine.[43] Pancreatic enzymes are needed for dietary zinc release; therefore, zinc absorption is affected by pancreatic disease.

Zinc absorption depends on the dietary amounts ingested and the potential presence of substances inhibiting absorption (fibre, calcium, iron or copper).[44] Absorption is also regulated by a copper-binding protein and other

divalent cations.[45] This protein is more sensitive to copper than to zinc. This means that in patients with Wilson's disease, the regular intake of zinc blocks copper absorption in the intestine.[46]

Zinc is transported bound to albumin and absorbed by peripheral tissue and the liver, where it is stored. The main route of Zn excretion is through feces, whereas only 2% is excreted through urine.[41]

Dietary reference values

According to EFSA (5), the DRV of Zn varies with age and sex, as shown in Table 1.

Dietary sources

The main dietary sources of Zn include red meats, poultry, oysters and other seafood, nuts, whole grains and dairy products.[5]

Food	Zn content (mg/ration*)	%DRV**
Oysters	74	493
Beef	7	47
Crab	6.5	43
Grains	3.8	25
Lobster	3.4	23
Pork meat	2.9	19
Poultry	2.4	16
Cashew nuts	1.6	11
Cheese	1.2	8
Milk (1 glass)	1	7

(*) Ration: 100 g of edible portion

(**) DRV taken as a reference: 15 mg/day.[46]

Causes and effects of inappropriate intake

It is estimated that 45% of adults in USA ingest an inadequate amount of Zn (48). Zinc deficiency (plasma concentrations below 50 mg/100 mL) can be caused by insufficient intake, intestinal absorption problems, substantial blood loss, and other health problems. Zn deficiency is also common in the following situations:[48]

- Vegetarianism: Vegetarian diets are usually rich in phytates, which reduce Zn absorption and increase the needs of vegetarians by up to 50%.[49]
- Alcoholism: Alcohol reduces Zn absorption and increases urinary Zn excretion. The variety and amount of food ingested by alcoholics is low and their dietary Zn intake is generally poor.[50]
- Digestive disorders (ulcerative colitis, Crohn's disease, or patients undergoing gastrointestinal surgery). The amount of Zn absorbed is reduced as a result of elevated Zn excretion.[51]
- Severe or chronic diarrhoea of any etiology.[52]
- Liver cirrhosis or Wilson's disease.[46]

Zinc deficiency has been suggested to affect growth in babies and children, sexual development in adolescents, and cause impotence in men. It is also related to hair loss, diarrhoea, eye and skin lesions and anorexia.[41]

The maximum tolerated intake of Zn is 25 mg/day.[53] Signs of excess Zn intake include nausea, vomiting, abdominal pain, loss of appetite, colic, diarrhoea and headaches and impaired copper absorption.[54]

Review of the evidence for Zn supplementation.

Common cold

Zn inhibits rhinovirus replication and seems to counter the activity of other respiratory viruses such as respiratory syncytial virus.[55] There is controversy on the efficacy of Zn in reducing the duration or severity of cold symptoms. Also, its intake is associated with a high incidence of adverse effects.

A systematic review of 17 trials involving 2,121 patients revealed that consuming Zn reduced the duration of symptoms (mean difference: 1.65 days, 95%CI: -2.5 to -0.8). Subgroup analysis showed a reduction in the duration of symptoms in adults (difference btw. means: -2.63 days, 95%CI: -3.69 to -1.58), but not in children (mean difference: 0.26 days, 95%CI: -0.78 to 0.25). Adverse events included bad taste (RR 1.65, 95%CI: 1.27 to 2.16) and nausea (RR 1.64; 95%CI: 1.19 to 2.27), which were frequent.[56]

The effects of Zn differed across formulations. According to a meta-analysis[57] where different formulations were compared, zinc acetate was more effective than zinc gluconate or zinc sulfate. Doses of Zn acetate above 75 mg were more effective than low doses, with a 42% reduction in the duration of cold (95%CI: 35% to 48%). In contrast, a meta-analysis of 7 randomized trials in 575 patients showed no differences in the efficacy of Zn acetate tablets in reducing the duration of cold, as compared to Zn gluconate.[58] Overall, the benefit-risk balance is unclear.

Pressure ulcers

A Cochrane review provided no evidence supporting that arterial or venous ulcers in the legs improve with oral Zn supplementation. This review included six trials of which four included patients with venous ulcers, one was related to pressure ulcers and another was focused on mixed ulcers. No statistically significant differences were

observed in relation to ulcer healing (RR 1.22; 95%CI: 0.88 to 1.68).[59]

Tinnitus

Zn is involved in cochlear physiology and auditory system synapses; therefore, Zn supplementation might be helpful for tinnitus. In contrast, a Cochrane review of three randomized trials comparing Zn supplementation vs. placebo provided no evidence on the benefit of oral Zn supplementation for tinnitus.[60]

Diarrhoea

Dietary Zn supplements help reduce the symptoms and duration of diarrhoea in children living in third World countries, many of whom have Zn deficiency or malnutrition.[61] For these children, the World Health Organization (WHO) recommends Zn supplementation for a period of 10 to 14 days (20mg/daily, or 10 mg/daily for children younger than 6 months).[62]

Depression

Several hypotheses have been proposed to explain the relationship between Zn and depression. The evidence suggests potential benefits of Zn supplementation in monotherapy or as add-on therapy to conventional antidepressants. Yet, the studies published are methodologically flawed due to their heterogeneity. In addition, the overall combined effect of Zn could not be estimated and further research is needed to confirm this hypothesis.[63]

Age-related macular degeneration (AMD)

Progression of early AMD could be prevented by Zn supplementation. A meta-analysis[64] revealed that antioxidant multivitamin supplements reduced the probability of progression to late AMD (0.83; 95%CI: 0.70 to 0.98; three studies; moderate evidence quality). AREDS[65] and AREDS2 studies were included in this systematic review.[66] The five-year AREDS study demonstrated a statistically significant benefit (OR 0.72; 95%CI: 0.58 to 0.90) of antioxidant (vitamin C, E and beta-carotene) plus zinc supplementation in the progression of early AMD. The doses administered largely exceeded the DRVs established for these elements. Thus, the daily dose was 500 mg (5 times the DRV) for vitamin C; 400 UI (13 times the DRV) for vitamin E; 15 mg for beta carotene; and 80 mg (6 times the DRV) for zinc. The administration of beta carotene can increase the risk for lung cancer in smokers.[67] Therefore, replacement of beta carotene with other carotenoids should be considered in smokers and recent ex-smokers. No significant adverse events associated with these combinations were reported. Blood tests (lipid profile and hematocrit) remained constant during the five years of follow-up. The AREDS2 study –of 4.7 years of duration– showed that replacement of beta carotene with Lutein and Zeaxanthin and a lower dose of Zn (25mg) had no negative effects on patients. No significant adverse events associated with these treatments were reported. No differences were observed in mortality [HR for the lutein/zeaxanthin arms vs. non-lutein/zeaxanthin was 0.92 (95%CI: 0.70 to 1.21)].

Although they seem to provide some benefit, further studies are needed that support the recommendation of oral Zn supplementation for AMRD. Important aspects such as the most effective dose and optimal duration of the treatment are still unclear.

Pregnancy and lactation

Low serum Zn levels are associated with suboptimal pregnancy outcomes such as prolonged labor, postpartum atonic hemorrhage, pregnancy-induced hypertension, preterm delivery and full-term pregnancies, although many of these associations have not yet been established. A systematic review of 21 randomized trials using Zn supplements vs. placebo/non-treatment showed that Zn supplementation reduced the rate of pre-term labors slightly (RR 0.86; 95%CI: 0.76 to 0.97; 16 trials involving 7637 women). Most data were collected from patients from developing countries[68].

A Cochrane review[69] revealed that these studies were not large enough and none of them provided data on primary endpoints: maternal morbidity (febrile illness, respiratory tract infection, diarrhoea), adverse effects of micronutrients within three days after receiving supplementation, infant mortality (defined as the death of a child before the first birthday).

Therefore, no evidence is available that Zn supplementation during pregnancy and lactation provides significant benefits.

Drug interactions

Zn supplements can interact with other drugs such as quinolones[70,71] or tetracyclines.[72,73] The reason is that antibiotics and Zn ion form an insoluble compound, thereby reducing their absorption. Therefore, these elements should not be taken simultaneously. Antibiotics should be ingested 4 hours before or 4-6 hours after taking the Zn supplement.

Zn supplements or Zn-containing multivitamin formulations and dolutegravir should be taken apart (minimum two hours after or six hours before), as they can interfere with dolutegravir absorption, thereby reducing serum concentrations.[37,74]

Contraindications

Hypersensitivity to the active component and excipients included.

Zn supplements available on the Spanish market

The dietary Zn supplements are available on the market include zinc gluconate, zinc acetate, zinc sulfate and zinc oxide.

Pharmaceutical forms available on the Spanish market*	Zinc (mg)
Elevit®, 30 film-coated tablets	7.5 mg/capsule
Hidropolivit 'a' mineral®, 30 chewable tablets	1 mg/capsule
Oftan Macula®, 90 capsules	7.5 mg/capsule
Sulfato de zinc NM® 250 mg, 90 capsules	15 mg/capsule
Wilzin® 25 mg, 250 capsules	25 mg/capsule
Wilzin® 50 mg, 250 capsules	50 mg/capsule
Zinc Arkovital®, 50 capsules	3.8 mg/capsule

(*) Data extracted from BOTPLUS®.[40]

Many multivitamin formulations contain Zn.

Selenium

Selenium (Se) is a necessary, albeit not nutritionally essential, trace element. Se is found in the organism as selenoproteins and has antioxidant properties.[75]

Dietary reference values

According to EFSA,[3] the quantification of Se content in food is difficult. As a result, food labels are often inaccurate, thereby leading to inexact estimates of Se intake. Reference values are shown in table 1.

Dietary sources

Food groups supplying Se include grains, fish, meat and dairy products.[3]

Main dietary sources of Selenium	Se content (µg/ration)	%DRV*
Brazil nuts (6-8 nuts)	544	777
Tuna	92	131
Canned sardines	45	64
Roast ham	42	60
Caridean shrimp	40	57
Beef (1 steak)	33	47
Turkey	31	44
Chicken	22	31
Ricotta-style cheese	20	29
Rice	19	27

(*) Ration. 100 g of edible portion.

(**) DRV taken as a reference: 70 µg/day (adults and children older than 4 yrs)[76]

Causes and effects of inappropriate intake

Se deficiency is uncommon and can rarely use a health problem. Deficiencies have been observed in vegans, selenium-deficient soils, long-term hemodialysis, HIV or episodes of diarrhoea and malabsorption.[76]

HIV patients show decreasing levels of Se as the disease progresses.[77]

The most frequent characteristics of Se toxicity (selenosis) include frailty and hair and nail loss. Other signs include gastrointestinal alterations, skin rash and garlic breath, fatigue, irritability and nervous system alterations. Only a few studies have been published on Se toxicity. A study performed in China in a sample of 380 subjects showed that the onset of signs of Se toxicity occurs at blood concentrations above 100 µg/dL (12.7 µmol/L), which corresponds to a Se intake > 850 µg/day.[78]

The CODING study revealed a significant inverse correlation between dietary Se intake and obesity regardless of age, total caloric intake, physical activity, smoking, alcohol use, medication and menopause.[79]

Review of the evidence for Se supplementation

Cancer

For its antioxidant properties, Se could play a role in the prevention of cancer, DNA repair, and immune and endocrine activity.[80-82]

Some observational and epidemiological studies have shown a negative correlation between dietary Se intake and the risk for some types of cancer such as colorectal, prostatic, lung, bladder, skin, esophageal and gastric cancer. However, no association has been observed between Se and breast cancer. Nevertheless, studies have limitations and their results should be interpreted with caution.[83]

Contradictory results have been obtained in controlled, randomised trials where Se supplementation was used for cancer prevention. Well designed randomised trials are needed to confirm the protective effects of Se against cancer.[84]

Cardiovascular disease

Only a few studies have been performed to assess the effects of Se supplementation on cardiovascular disease. Moreover, the results reported are not conclusive. A review of 25 observational studies and 6 randomised trials demonstrated that a 50% increase in Se concentrations (≥ 80 µg of selenium/L) was associated with a 24% reduction in the risk for coronary disease. The relative risk associated with a 50% increase of Se concentrations was 0.76 (95%CI 0.62 to 0.93).[85]

Nevertheless, other observational studies did not provide evidence of a significant association between Se concentrations and the risk for heart disease or cardiac death. Other studies showed that high Se concentrations were associated with a greater risk for cardiovascular disease.[86-88]

Therefore, no evidence has been provided so far to support the use of Se supplementation for the prevention of heart disease.[89] More trials are needed to better understand the effects of Se on cardiovascular health.[90]

Cognitive impairment

Low levels of selenium (<0.96 µmol/L) have been associated with an increased risk for cognitive impairment,[91] but there is no evidence has been provided supporting that Se alone or in multivitamin compounds prevents age-related cognitive impairment.[92, 93]

Due to their role in human physiology, minerals are attributed to have medicinal properties, without scientific support.

Thyroid disease

Se concentrations are higher in the thyroid gland. As it occurs with iodine, Se plays a relevant role in the synthesis and metabolism of the thyroid hormone. Inconclusive results have been obtained in relation to the contribution of Se supplementation in the prevention or treatment or thyroid disease, hypothyroxinemia during pregnancy and postpartum thyroid dysfunction.[94-96]

Pregnancy and lactation

As European nutritional recommendations regarding Se supplementation during pregnancy are inconsistent, an official recommendation cannot be made.[3]

Drug interactions

Cisplatin. There is evidence that Se supplementation can reduce cistaplin toxicity.[97] However, a Cochrane review revealed that evidence on the efficacy of Se supplementation in the prevention of chemotherapy side effects is not robust.[98]

A treatment switch may be required as a result of interaction between Se and dolutegravir indicated in combination for HIV; Se and eltrombopag indicated for the treatment of anemia.[100] For their chelating action, oral multivitamin formulations containing polyvalent cations like selenium may decrease serum dolutegravir and eltrombopag concentrations and reduce their efficacy.[101]

Contraindications

Hypersensitivity to the active component and excipients included.

Se supplements available on the Spanish market

Selenium can be found in the form of L-selenomethionine in mineral multivitamin supplements, antioxidant formulas and other dietary supplements. Also, Se is present in beer yeast in the form of Selenium-rich baker yeast.

Pharmaceutical forms available on the Spanish market*	Selenium (mcg)
Selenio Arkopharma®, 50 capsules	35 mcg/cápsula
Selenio Select®, 30 capsules	105 mcg/cápsula
Selenio NM®, 90 capsules	50 mcg/cápsula

(*) Data extracted from BOTPLUS®.[40]

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Conclusions:

No conclusive evidence has yet been provided on the beneficial effects of oral magnesium, zinc and selenium supplementation in subjects with a normal nutritional status:

Statistically significant results have only been obtained for the reduction of blood pressure by magnesium supplementation, but its effects are clinically irrelevant.

In early AMD, a combination of vitamin and mineral zinc-containing compounds reduces the risk for progression to advanced AMD. However, the contribution of each component has not been determined separately. Although this effect has been consistently demonstrated in several studies, more research is needed to determine the dose and duration of zinc supplementation.

There is no robust evidence to suggest that selenium supplementation is beneficial for the general population or people with health problems. Selenium deficiency by itself rarely causes health problems or disease and can be prevented by a balanced diet.

References

1. Sassan Pazirande MD. Overview of dietary trace minerals. Post TW, ed. UpToDate . Waltham, MA: Uptodate Inc.

2. OCU: OCU advierte de la generalización del consumo de suplementos alimenticios innecesarios [Internet] (Actualizado 23 de enero de 2018) (Consultado 20 de julio de 2018).

3. EFSA NDA Panel, 2014. Scientific Opinion on Dietary Reference Values for selenium. EFSA J. 2014;12(10):3846.

4. EFSA NDA Panel, 2015. Scientific Opinion on Dietary Reference Values for magnesium. EFSA J. 2015;13(7):4186.

5. EFSA NDA Panel, 2014. Scientific Opinion on Dietary Reference Values for zinc. EFSA J. 2014;12(10):3844.

6. Carbajal Azcona Á. Manual de Nutrición y Dietética. 2013;1–367.

7. Cakmak I, Yazici AM. Magnesium: A Forgotten Element in. Crop Production. Better Crops 2010;94(2):23-25.

8. NIH National Institutes of Health. Office of Dietary Supplements: Magnesium.

9. OCU: Suplementos alimenticios ¿para qué? [Internet] (Actualizado 23 de enero de2018) (Consultado 20 de julio de 2018)

10. Rodriguez Portillo M. Trastornos del calcio, el fosforo y el magnesio. Nefrol al día. 2011;25:201–219. doi: 10.3265/Nefrologia.2010.pub1.ed35.chapter1836.

11. Dickinson HO, Nicolson D, Campbell F, Cook J V, Beyer FR, Ford GA, et al. Magnesium supplementation for the management of primary hypertension in adults. Cochrane Database Syst Rev 2006; 3. CD004640. DOI: 10.1002/14651858.CD004640.pub2.

12. Kass L, Weekes J, Carpenter L. Effect of magnesium supplementation on blood pressure: A meta-analysis. Eur. J. Clin. Nutr. 2012;66:411–418.

13. Zhang X, Li Y, Del Gobbo LC, Rosanoff A, Wang J, Zhang W, et al. Effects of Magnesium Supplementation on Blood Pressure: A Meta-Analysis of Randomized Double-Blind Placebo-Controlled Trials. Hypertens. 2016;68(2):324–333.

14. National Clinical Guideline Centre. Hypertension: the Clinical Management of Primary Hypertension in Adults. London: National Clinical Guideline Centre (UK), 2011 Aug (updated 2016 November): CG127.

15. Kim DJ, Xun P, Liu K, Loria C, Yokota K, Jacobs DR, et al. Magnesium intake in relation to systemic inflammation, insulin resistance, and the incidence of diabetes. Diabetes Care. 2010;33(12):2604–2610.

16. Ross AC, Caballero B, Cousins RJ, Tucker KL, Ziegler TR. Modern nutrition in health and disease: Eleventh edition. Wolters Kluwer Health Adis (ESP), 2012. 1616 p.

17. Kao WH, Folsom a R, Nieto FJ, Mo JP, Watson RL, Brancati FL. Serum and dietary magnesium and the risk for type 2 diabetes mellitus: the Atherosclerosis Risk in Communities Study. Arch Intern Med. 1999;159(18):2151–2159.

18. Larsson SC, Wolk A. Magnesium intake and risk of type 2 diabetes: a meta-analysis. J Intern Med. 2007 Aug;262(2):208-14.

19. Dong JY, Xun P, He K, Qin LQ. Magnesium intake and risk of type 2 diabetes: meta-analysis of prospective cohort studies. Diabetes Care. 2011 Sep;34(9):2116-22. doi: 10.2337/dc11-0518.

20. Mutlu M, Argun M, Kilic E, Saraymen R, Yazar S. Magnesium, Zinc and Copper Status in Osteoporotic, Osteopenic and Normal Post-menopausal Women. J Int Med Res. 2007;35(5):692–5.

21. Teigen L, Boes CJ. An evidence-based review of oral magnesium supplementation in the preventive treatment of migraine. Cephalalgia. 2015;35(10):912-22.

22. Mauskop A, Varughese J. Why all migraine patients should be treated with magnesium. J Neural Transm. 2012;119(5):575-9.

23. Facchinetti F, Sances G, Borella P, Genazzani AR, Nappi G. Magnesium Prophylaxis of Menstrual Migraine: Effects on Intracellular Magnesium. Headache J Head Face Pain. 1991;31(5):298–301.

24. Peikert A, Wilimzig C, Köhne-Volland R. Prophylaxis of migraine with oral magnesium: Results from a prospective, multi-center, placebo-controlled and double-blind randomized study. Cephalalgia. 1996;16(4):257–263.

25. Pfaffenrath V, Wessely P, Meyer C, Isler HR, Evers S, Grotemeyer KH, et al. Magnesium in the prophylaxis of migraine-a double-blind placebo-controlled study. Cephalalgia. 1996;16(6):436–40.

26. Bigal ME, Bordini CA, Tepper SJ, Speciali JG. Intravenous magnesium sulphate in the acute treatment of migraine without aura and migraine with aura. A randomized, double-blind, placebo-controlled study. Cephalalgia. 2002;22(5):345–353.

27. Choi H et Parmar N. The use of intravenous magnesium sulphate for acute migraine: meta-analysis of randomized controlled trials. Eur J Emerg Med. 2014; 21(1):2-9

28. Migraine - treatment of acute attack in adults. In DynaMed Plus [database online]. EBSCO Information Services.

29. Derom M-L, Sayón-Orea C, Martínez-Ortega JM, Martínez-González MA. Magnesium and depression: a systematic review. Nutr Neurosci. 2013; 16:191-206.

30. Widmer J, Henrotte JG, Raffin Y, Bovier P, Hilleret H, Gaillard JM. Relationship between erythrocyte magnesium, plasma electrolytes and cortisol, and intensity of symptoms in major depressed patients. J Affect Disord. 1995;34(3):201–209.

31. Barragan-Rodríguez L, Rodríguez-Morán M, Guerrero-Romero F. Depressive Symptoms and Hypomagnesemia in Older Diabetic Subjects. Arch Med Res. 2007;38(7):752–756

32. Camardese G, De Risio L, Pizi G, Mattioli B, Buccelletti F, Serrani R, et al. Plasma magnesium levels and treatment outcome in depressed patients. Nutr Neurosci. 2012;15(2):78–84.

33. Derom M-L, Martínez-González M a, Sayón-Orea MDC, Bes-Rastrollo M, Beunza JJ, Sánchez-Villegas A. Magnesium intake is not related to depression risk in Spanish university graduates. J Nutr. 2012;142(6):1053–1059.

34. Makrides M, Crosby DD, Bain E, Crowther CA. Magnesium supplementation in pregnancy. Cochrane database Syst Rev. 2014; 4. CD000937. doi: 10.1002/14651858.CD000937.pub2.

35. Crowther CA, Brown J, McKinlay CJD, Middleton P. Magnesium sulphate for preventing pretermbirth in threatened preterm labour.Cochrane Database of Syst Rev. 2014; 8. CD001060.DOI: 10.1002/14651858.CD001060.pub2.

36. Magnesium salts. In: Lexi-Comp Online TM, Lexi-Drugs Online TM. Hudson (OH): Lexi.Comp, Inc.; Acceso via UptoDate 2 Ene 2018.

37. University of Liverpool. HIV Drug Interactions Website. HIV Drug Interactions. .

38. Sarafidis PA, Georgianos PI, Lasaridis AN. Diuretics in clinical practice. Part II: electrolyte and acid-base disorders complicating diuretic therapy. Expert Opin Drug Saf. 2010;9(2):259–273.

39. Magnogene® AEMPS. Ficha técnica.

40. Base de Datos de medicamentos del Consejo General de Farmacéuticos (Bot PLUS 2.0).

41. Rubio C, González Weller D, Martín-Izquierdo RE, Revert C, Rodríguez I, Hardisson A. El zinc: Oligoelemento esencial. Nutr Hosp. 2007;22:101–107.

42. Salgueiro MJ, Zubillaga M, Lysionek A, Sarabia MI, Caro R, De Paoli T, et al. Zinc as an essential micronutrient: A review. Nutr Res. 2000;20:737-55.

43. Lee HH, Prasad AS, Brewer GJ, Owyang C. Zinc absorption in human small intestine. Am J Physiol. 1989;256(1 Pt 1):G87-91.

44. Cousins RJ. Absorption, transport, and hepatic metabolism of copper and zinc: special reference to metallothionein and ceruloplasmin. Physiol Rev. 1985;65:238–309.

45. Bremner I, Beattie JH. Metallothionein and the Trace Minerals. Annu Rev Nutr. 1990;10(1):63–83.

46. Yuzbasiyan-Gurkan V Nostrant T, Cousins RJ, Brewer GJ. GA. Treatment of Wilson's disease with zinc: X. Intestinal metallothionein induction. J Lab Clin Med. 1992;120(3):380–6.

47. NIH National Institutes of Health. Office of Dietary Supplements: Zinc.

48. Briefel RR, Bialostosky K, Kennedy-Stephenson J. McDowell MA, Ervin RB, Wright JD. Zinc intake of the U.S. population: findings from the third National Health and Nutrition Examination Survey, 1988-1994. J Nutr. 2000 May;130(5S Suppl):1367S-73S.

49. Hunt JR. Bioavailability of iron, zinc, and other trace minerals from vegetarian diets. Am J Clin Nutr. 2003;78(3 Suppl):633-639.

50. Menzano E, Carlen PL. Zinc Deficiency and Corticosteroids in the Pathogenesis of Alcoholic Brain Dysfunction—A Review. Alcohol Clin Exp Res. 1994;18(4):895–901.

51. Hwang C, Ross V, Mahadevan U. Micronutrient deficiencies in inflammatory bowel disease: From A to zinc. Inflamm. Bowel Dis. 2012;18:1961–1981.

52. Fischer Walker CL, Black RE. Zinc for the treatment of diarrhoea: Effect on diarrhoea morbidity, mortality and incidence of future episodes. Int J Epidemiol. 2010;39(SUPPL. 1): 63-69.

53. Stefanidou M, Maravelias C, Dona A, Spiliopoulou C. Zinc: A multipurpose trace element. Arch Toxicol. 2006;80:1–9.

54. Prasad AS, Rabbani P, Brewer GJ, Schoomaker EB. Hypocupremia Induced by Zinc Therapy in Adults J Am Med Assoc. 1978;240(20):2166–2168.

55. Suara RO, Crowe JE, Jr. Effect of zinc salts on respiratory syncytial virus replication. Antimicrob Agents Chemother. 2004;48(3):783–790. Available from:

56. Science M, Johnstone J, Roth DE, Guyatt G, Loeb M. Zinc for the treatment of the common cold: a systematic review and meta-analysis of randomized controlled trials. CMAJ. 2012;184(10):E551-561.

57. Hemilä H. Zinc lozenges may shorten the duration of colds: a systematic review. Open Respir Med J. 2011;5:51–8.

58. Hemilä H. Zinc lozenges and the common cold: a meta-analysis comparing zinc acetate and zinc gluconate, and the role of zinc dosage. JRSM Open. 2017;8(5):205427041769429.

59. Wilkinson EAJ. Oral zinc for arterial and venous leg ulcers. Cochrane database Syst Rev. 2014; 9. CD001273. DOI: 10.1002/14651858.CD001273.pub3

60. Person OC, Puga ME, da Silva EM, Torloni MR. Zinc supplementation for tinnitus. Cochrane Database Syst Rev. 2016; 11. CD009832.DOI: 10.1002/14651858.CD009832.pub2.

61. Lazzerini M, Wanzira H. Oral zinc for treating diarrhoea in children. Cochrane Database Syst Rev. 2016; 12. CD005436. DOI: 10.1002/14651858.CD005436.pub5.

62. WHO. Implementing the new recommendations of the clinical management of diarrhoea. Geneva: World Health Organization; 2006.

63. Lai J, Moxey A, Nowak G, Vashum K, Bailey K, McEvoy M. The efficacy of zinc supplementation in depression: Systematic review of randomised controlled trials. J Affect Disord. 2012;136(1-2):e31-e39.

64. Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. Cochrane Database Syst Rev. 2017; 7. CD000254. DOI: 10.1002/14651858.CD000254.pub4.

65. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol. 2001;119(10):1417–36.

66. Eye TA, Study D. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. JAMA. 2013;309(19):2005–15.

67. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med. 1994;330(15):1029–1035.

68. Ota E, Mori R, Middleton P, Tobe-Gai R, Mahomed K, Miyazaki C, et al. Zinc supplementation for improving pregnancy and infant outcome. Cochrane Database Syst Rev. 2015; 2. CD000230. DOI:10.1002/14651858.CD000230.pub5.

69. Abe SK, Balogun OO, Ota E, Takahashi K, Mori R. Supplementation with multiple micronutrients for breastfeeding women for improving outcomes for the mother and baby. Cochrane Database Syst Rev. 2016; 2. CD010647. DOI: 10.1002/14651858.CD010647.pub2.

70. Polk RE, Healy DP, Sahai J, Drwal L, Racht E. Effect of ferrous sulfate and multivitamins with zinc on absorption of ciprofloxacin in normal volunteers. Antimicrob Agents Chemother. 1989;33(11):1841–4.

71. Campbell N, Kara M, Hasinoff B, Haddara W, McKay D. Norfloxacin interaction with antacids and minerals. Br J Clin Pharmacol. 1992;33(1):115–6.

72. Penttilä O, Hurme H, Neuvonen PJ. Effect of zinc sulphate on the absorption of tetracycline and doxycycline in man. Eur J Clin Pharmacol. 1975;9(2–3):131–4.

73. Brion M, Lambs L, Berthon G. Metal ion-tetracycline interactions in biological fluids. Part 5. Formation of zinc complexes with tetracycline and some of its derivatives and assessment of their biological significance. Agents Actions. 1985;17(2):229–42.

74. Zinc salts. In: Lexi-Comp Online TM, Lexi-Drugs Online TM. Hudson (OH): Lexi.Comp, Inc.; Acceso via UptoDate 2 Ene 2018

75. Ross AC, Caballero B, Cousins RJ, Tucker KL, Ziegler TR. Modern nutrition in health and disease: Eleventh edition. 2012.

76. NIH National Institutes of Health. Office of Dietary Supplements: Selenium.

77. Stone CA, Kawai K, Kupka R, Fawzi WW. Role of selenium in HIV infection. Nutr Rev. 2010;68(11):671–81.

78. Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes: Vitamin C, Vitamin E, Selenium, and Carotenoids. National Academy Press, Washington, DC, 2000.

79. Wang Y, Gao X, Pedram P, Shahidi M, Du J, Yi Y, et al. Significant beneficial association of high dietary selenium intake with reduced body fat in the CODING study. Nutrients. 2016;8(1).

80. Rayman MP. Selenium and human health. Lancet. 2012;379: 1256-68.

81. Allen N, Appleby P. Plasma selenium concentration and prostate cancer risk: results from the European Prospective Investigation into Cancer and Nutrition (EPIC). Clin Nutr. 2008;(6):1–3.

82. Combs GF, Gray WP. Chemopreventive Agents: Selenium. Pharmacol Ther. 1998 Sep;79(3):179-92.

83. Dennert G, Zwahlen M, Brinkman M, Vinceti M, Zeegers MPA, Horneber M. Selenium for preventing cancer. Cochrane Database Syst Rev 2011; 5. CD005195. DOI: 10.1002/14651858.CD005195.pub2.

84. Bjelakovic G, Nikolova D, Simonetti RG, Gluud C. Systematic review: primary and secondary prevention of gastrointestinal cancers with antioxidant supplements. Aliment Pharmacol Ther. 2008;28(6):689–703.

85. Flores-Mateo G, Navas-Acien A, Pastor-Barriuso R, Guallar E. Selenium and coronary heart disease: a meta-analysis. Am J Clin Nutr. 2006;84(4):762–73.

86. Xun P, Liu K, Morris JS, Daviglus ML, He K. Longitudinal association between toenail selenium levels and measures of subclinical atherosclerosis: The CARDIA trace element study. Atherosclerosis. 2010;210(2):662–667.

87. Bleys J, Navas-Acien A, Guallar E. Serum selenium levels and all-cause, cancer, and cardiovascular mortality among US adults. Arch Intern Med. 2008;168(4):404–410.

88. Bleys J, Navas-Acien A, Laclaustra M, Pastor-Barriuso R, Menke A, Ordovas J, et al. Serum selenium and peripheral arterial disease: Results from the national health and nutrition examination survey, 2003-2004. Am J Epidemiol. 2009;169(8):996–1003.

89. Rees K, Hartley L, Day C, Flowers N, Clarke A, Stranges S. Selenium supplementation for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013; 1. CD009671.DOI: 10.1002/14651858.CD009671.pub2.

90. Leighton D, Goua M, Dolan E, Burgess K, Bermano G. The role of selenium supplementation in cardiovascular disease prevention: an in vitro study to identify the molecular mechanism(s). Proc Nutr Soc. 2015;74.

91. Berr C, Balansard B, Arnaud J, Roussel AM, Alpérovitch A. Cognitive decline is associated with systemic oxidative stress: the EVA study. Etude du Vieillissement Artériel. J Am Geriatr Soc. 2000;48(10):1285–91.

92. Emmanuelle Kesse-Guyot, Léopold Fezeu, Claude Jeandel, Monique Ferry, Valentina Andreeva, Hélène Amieva, Serge Hercberg, Pilar Galan; French adults' cognitive performance after daily supplementation with antioxidant vitamins and minerals at nutritional doses: a post hoc analysis of the Supplementation in Vitamins and Mineral Antioxidants (SU.VI.MAX) trial–, The American Journal of Clinical Nutrition, Volume 94, Issue 3, 1 September 2011, Pages 892–899.

93. Kane RL, Butler M, Fink HA, et al. Interventions to Prevent Age-Related Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer's-Type Dementia [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2017 Mar. (Comparative Effectiveness Reviews, No. 188.)

94. Derumeaux H, Valeix P, Castetbon K, Bensimon M, Boutron-Ruault MC, Arnaud J, et al. Association of selenium with thyroid volume and echostructure in 35- to 60-year-old French adults. Eur J Endocrinol. 2003;148(3):309–15.

95. Rasmussen LB, Schomburg L, Köhrle J, Pedersen IB, Hollenbach B, Hög A, et al. Selenium status, thyroid volume, and multiple nodule formation in an area with mild iodine deficiency. Eur J Endocrinol. 2011;164(4):585–90.

96. Reid SM, Middleton P, Cossich MC, Crowther CA. Interventions for clinical and subclinical hypothyroidism in pregnancy. Cochrane Database Syst Rev. 2010; 7. CD007752. DOI: 10.1002/14651858.CD007752.pub2.

97. Hu YJ, Chen Y, Zhang YQ, Zhou MZ, Song XM, Zhang BZ, et al. The protective role of selenium on the toxicity of cisplatin-contained chemotherapy regimen in cancer patients. Biol Trace Elem Res. 1997;56(3):331–41.

98. Dennert G, Horneber M. Selenium for alleviating the side effects of chemotherapy, radiotherapy and surgery in cancer patients. Cochrane Database Syst Rev. 2006; 3. CD005037. DOI:10.1002/14651858.CD005037.pub2.

99. Taha H, Das A, Das S. Clinical effectiveness of dolutegravir in the treatment of HIV/AIDS. Infect Drug Resist. 2015;8:339-352.

100. Eltrombopag (Revolade®). AEMPS: Ficha técnica.

101. Selenium salts. In: Lexi-Comp Online TM, Lexi-Drugs Online TM. Hudson (OH): Lexi.Comp, Inc.; Acceso via UptoDate 2 Ene 2018.

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