Controversial Effect of Vitamin E Supplementation in Subjects with Down Syndrome

Iris Samarra Mestre. Grau Ciències biomèdiques, 2015
Universitat Autònoma de Barcelona

Universitat Autònoma de Barcelona

Introduction

Down syndrome (DS) is caused by a total or partial trisomy of chromosome 21 in humans.

The overexpression of the enzyme Superoxide dismutase (SOD) located in chromosome 21 leads to an elevated oxidative stress which contributes to the pathology of DS (see Figure 1).

Using antioxidants to reduce oxidative stress levels is a promising approach for slowing or preventing DS associated features and maybe improving cognitive function.

Vitamin E is a lipid-soluble antioxidant that protects from lipid peroxidation and DNA damage. The intake of vitamin E might be useful in preventing cognitive deterioration in DS.

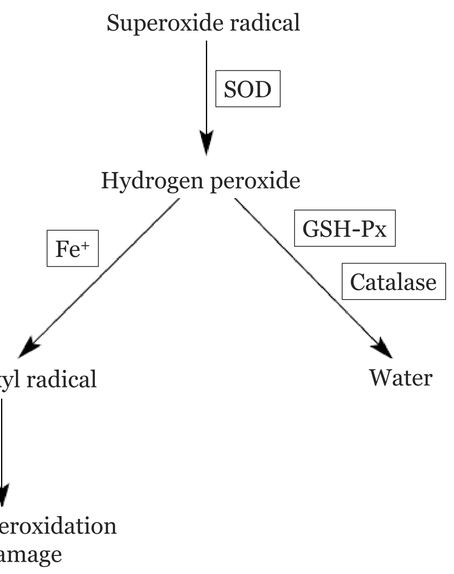

Figure 1 Pathway from the increase of SOD to the generation of oxidative damage. Adapted from Ani *et al.* (2000)

Objective

- Review the studies that have been done on the subject of supplementation with vitamin E in patients with DS and its current state.

Materials and Methods

Search on the following sites:

- PubMed: Scientific articles.
- www.clinicaltrials.org: Actual clinical trials on the subject.

Key words: "Vitamin E", "Down syndrome", "antioxidant", "oxidative stress".

Results of Vitamin E Supplementation Studies

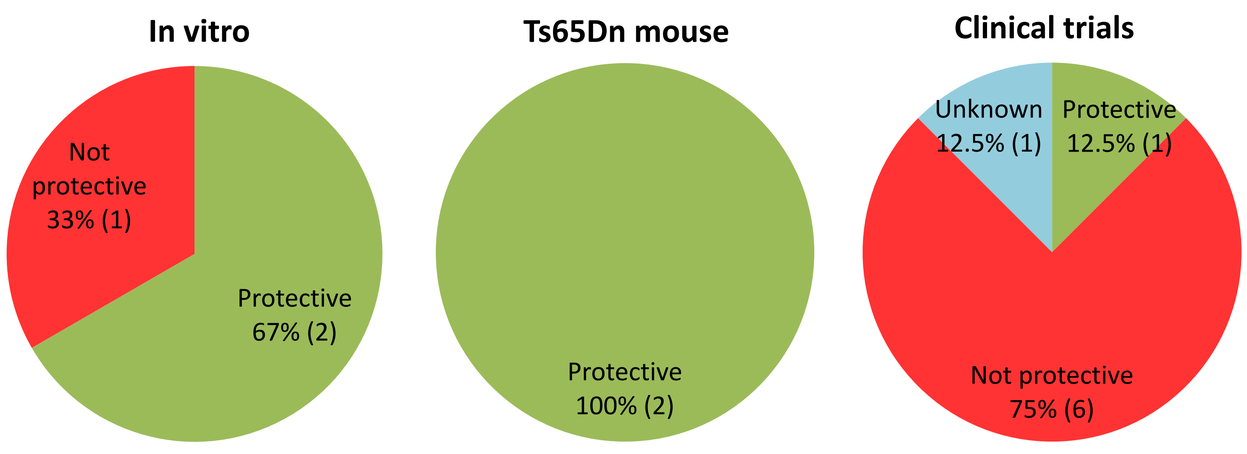

Figure 3 Results of *in vitro* (3), animal model (2) and clinical studies (8). In 67% of *in vitro* studies, 100% of animal studies and 12.5% of the clinical trials, the supplementation with vitamin E was protective. One clinical trial has not published the results yet.

***In vitro* studies**: Vitamin E is neuroprotective, increases neuronal survival and protects from chromosomal damage.
Animal studies: Vitamin E delays cognitive decline in aged mice and improves cognitive deficits in newborn mice.
Clinical trials: Vitamin E attenuates the systemic oxidative stress.

***In vitro* studies**: Vitamin E can be apoptotic.
Clinical trials: Vitamin E does not improve cognitive, psychomotor or language development.

A completed **phase III clinical trial** (Dalton A, 2012) has not published the results yet. This well-designed trial could provide definitive evidence as to whether vitamin E can restore cognitive function in an aging population with DS.

Vitamin E: Isomers and toxicity

Vitamin E consists of four tocopherol isomers (α, β, γ, δ) and four tocotrienol isomers (α, β, γ, δ). They are closely related chemically (see Figure 2) but they differ in their biological effectiveness.

- Radical-scavenging activity: **α-tocopherol** > other tocopherols > tocotrienols >> chemically synthesized α-tocopherol

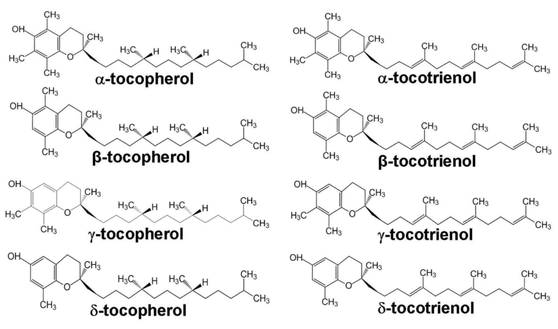

Figure 2 Natural R,R,R-tocopherols and R,R,R-tocotrienols. Adapted from Cook-Mills, J.M. (2013)

- Mixtures of different forms of vitamin E have a **broader range** of free-radical-scavenging abilities.
- High doses of Vitamin E can have **toxic effects**, including apoptotic activity (tocotrienols more than tocopherols), adverse effects on offspring (high maternal α-tocopherol) and hemorrhagic toxicity.

Discussion

Despite the mostly promising results of *in vitro* and animal studies, interventional studies of vitamin E supplementation in DS human subjects have not been conclusive.

Possible explanation for the lack of effect	Solutions
Small sample size	Big sample size
Short-term supplementation	Long-term supplementation
Old individuals	Young individuals
Not enough vitamin E crosses the blood-brain barrier	Supplement with vitamin E and C*
Outcome measures not appropriate	Standardize outcome measures
Dose	More basic research
Isomeric form of vitamin E	More basic research

Table 1 Problems and solutions of clinical research done on the subject of vitamin E supplementation in DS. *Vitamin C seems to improve other compounds to cross the blood-brain barrier.

Conclusions

- There is no consistent proof that vitamin E improves the outcome in DS.
- Antioxidant intervention should start soon after birth, before the chronic oxidative damage is already installed.
- Well-designed research needs to be done to select the right isomer and dose of vitamin E.
- Theoretically, the best treatment choice would be the natural α-tocopherol combined with either other isomers or vitamin C.
- There are potential adverse effects from high doses and prolonged supplementation. The safety of vitamin E should be evaluated.
- Until we have clear evidence of the benefits of vitamin E supplementation, parents should be discouraged of giving it to their children with DS.

References

Ani, C., Grantham-McGregor, S. & Muller, D. Nutritional supplementation in Down syndrome : theoretical considerations and current status. *Dev. Med. Child Neurol.* **42**, 207–213 (2000)

Cook-Mills, J. M. Isoforms of Vitamin E Differentially Regulate PKC α and Inflammation: A Review. *J. Clin. Cell. Immunol.* **4**, (2013)

Dalton, A. Multicenter Vitamin E Trial in Aging Persons With Down Syndrome (2012). Clinical trial NCT01594346.