Vitamin E and gene interactions

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Outline

• One size does not fit all: role of polymorphism

• Vitamin E is an established essential micronutrient, as defined in daily intake requirements, which has to be provided to the human body on a regular basis

• Emerging science suggests vitamin E to convey health benefits which are not addressed / covered by the daily requirements:
  • Vitamin E & haptoglobin 2-2
  • Vitamin E & Catechol-O-Methyltransferase (COMT) variant rs4680

• What is the prudent way forward to benefit human health by vitamin E?
Today’s nutrition: One size does not fit all. Not everyone responds similarly to food: People are “different” by polymorphisms
Nutrigenomics will help to understand individual requirements

The science of nutrigenomics seeks to provide a molecular understanding for how common dietary ingredients (i.e., nutrients) affect health by altering the expression and/or conformational structures of an individual’s genetic makeup. Turning on and off your genes that control diseases!
DNA is not your destiny
Focus of the talk will be on vitamin E and out of the many nutrient gene interaction on two relevant once on which new science demonstrate health benefits
Vitamin E is a powerful chain-breaking antioxidant. Once oxidized, it can be regenerated by vitamin C.

Due to its lipophilic nature, vitamin E localizes to lipid compartments, such as cell membranes (prevention of peroxidation of lipids and oxidation of proteins).

Furthermore, vitamin E depletion and repletion affects gene expression in vitro in cells and in vivo in animal models, indicating broader effects than just protection from oxidation.

Incorporation of vitamin E into cellular membranes can alter the activity of membrane-associated proteins and thereby changes signal transduction pathways.

EFSA Health Claim in 2011: “Vitamin E contributes to the protection of cells from oxidative stress”
Nutrient requirements/recommended intakes

Dietary reference values for nutrient intake are:

- Science-based
- Dependent on the existing data available
- Country or institution specific
- Potentially politically driven
- Reflect ‘eating cultures’
Current RDAs for vitamin E are based on markers of cell membrane integrity

→ 1. Lysis of red blood cells
→ 2. PUFA intake

- Lysis of erythrocytes are associated with decreases erythrocyte survival (which can be corrected by vitamin E supplementation)
- From research in a limited number of people, reported in the seventies a vitamin E serum level of 12 µmol/L was derived to prevent hemolysis
- To achieve a serum level of 12 µmol/L α-tocopherol an intake of 12 mg vitamin E is required
- 12 mg vitamin E is the intake to meet the requirements of 50% of the population (EAR) and 15 mg vitamin E will suffice to meet the needs of 97% of the population (RDA)
- Vitamin E requirements vary from 15 to 25 mg/day or more depending on PUFA intake
  → Additional vitamin E needs should become part of RDA

A higher intake of nutrients beyond nutritional requirements may provide additional benefits in defined groups

RDA = Recommended Dietary Allowance
EAR = Estimated Average Requirement

Institute of Medicine 2000
People are different, ..!
... and, emerging science provides new insights!

- There may be different needs, which cannot be covered by the RDA approach.
- In addition, we have a better understanding about the human genome.
- There is evidence that the genotype can be key to a response of a given nutrient.
- i.e., 10-20 mio Single Nucleotide Polymorphisms (SNP) believed to exist (ca 4 mio known).
- Two examples where the genotype can make a significant difference in human nutrition will be highlighted:
  - Vitamin E & haptoglobin 2-2
  - Vitamin E & COMT variant rs4680
Epidemiological evidence for vitamin E benefits

- Lower plasma level of vitamin E has been reported in type 2 diabetic subjects compared to controls.

- Prospective epidemiological studies demonstrate that high serum vitamin E was associated with decreased risk of type 2 diabetes.

- Evidence from various observational human studies indicated that vitamin E has beneficial effects on the cardiovascular system.

- At least five studies reported that increased consumption of vitamin E is associated with decreased risk for heart attack or death from cardiovascular disease.

- It was therefore hypothesized that vitamin E supplementation could reduce the risk for cardiovascular events.

Salonen et al. (1995)
Maxwell et al. (1997)
However, most RCTs find no vitamin E benefits for cardiovascular health

- Several randomized clinical trials have been performed to examine the efficacy of vitamin E in improving human health.
- Surprisingly, the results from the trials did not detect a consistent benefit of vitamin E supplementation on cardiovascular health.

<table>
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<th>Study</th>
<th>Dose</th>
<th>Duration</th>
<th>Cases</th>
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<tr>
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<tr>
<td>CHAOS</td>
<td>&gt;400</td>
<td>1.3</td>
<td>105</td>
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<tr>
<td>GISSI</td>
<td>300</td>
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<tr>
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<tr>
<td>Total</td>
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**Meta-Analysis of the effect of Vitamin E on Myocardial Infarction, Stroke, or Death from Cardiovascular Causes in large trials** (modified from Yusuf et al. 2000)

- **Relative Risk:**
  - ATBC: 0.6
  - CHAOS: 0.8
  - GISSI: 1.2
  - HOPE: 1.4
  - Total: 0.97 (0.92-1.02)

**Favors vitamin E** ➡️ **Favors placebo**
Several randomized clinical trials supplementing vitamin E failed to corroborate the epidemiological findings.

However, new research provides an insight into the apparent disagreement.

While no effects are observed in the general population; specific sub-populations with specific genetic make-up may profit from vitamin E.
Vitamin E reduces cardiovascular events in diabetics and Hp 2-2 genotype

- Haptoglobin (Hp) is a protein that scavenges free hemoglobin in the blood.
- The Hp gene exists in two variants, the Hp1 and the Hp2 variant. In Western societies, 36% have haptoglobin genotype 2-2 (Hp 2-2)
- Diabetic individuals with Hp 2-2 have a marked increased oxidative stress
- Increased risk for cardiovascular events has been linked to Hp 2-2 genotype in diabetics.

Vitamin E supplementation at a dose of 400 mg reduces and normalizes the risk for cardiovascular events in diabetics with Hp 2-2

Results from the ICARE study (Milman 2008) (RCT with 1434 diabetes patients with Hp2-2 genotype, receiving placebo or 400 IU vit E/day)

Kaplan Meier-Plot of the composite end-point in Hp 1-1 & Hp 2-1 DM Individuals compared with Hp 2-2 individuals receiving placebo or vitamin E
Findings from the ICARE Study are supported by results from other large-scale RCTs

- N = 2545 women and 6996 men 55+ yrs, CVD or diabetes + one other risk factor, 400 IU/d vitamin E or ACE-inhibitor or placebo for 4.5 years, composite endpoint

- Vitamin E had no apparent effect on cardiovascular outcomes

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Vitamin E</th>
<th>Placebo</th>
<th>Odds Ratio</th>
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<tr>
<td></td>
<td>Events</td>
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<td>4.4.1 Hp 2-2</td>
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<tr>
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</tr>
<tr>
<td>Total events</td>
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Proposed vitamin E function in diabetic Hp 2-2 individuals

- **Haptoglobin** binds and inhibits the oxidative activity of free hemoglobin (Hb), and targets it for clearance from the blood.

- The **Haptoglobin 2** protein forms aggregates which affects its function. **Hemoglobin** is not cleared as efficiently.

- Furthermore, **Hb-Hp2-2** complex binds to HDL, oxidizes proteins and lipids in HDL and renders HDL dysfunctional and prothrombic.

- Vitamin E protects lipids and proteins in HDL from oxidation.
Diabetes is a huge and growing public health problem

1. At least 1 in 10 deaths among adults is attributable to diabetes
2. Diabetes deaths are projected to double between 2005 and 2030
3. >80% of diabetes deaths occur in low- and middle-income countries

Genetic variants of the Catechol-O-Methyltransferase Modify the Risk of Cardiovascular Diseases (Kathryn T. Hall et al, 2014, Arterioscler Thromb Vasc Biol)

- COMT degrades catecholamines by catalyzing the transfer of a methyl group donated by S-adenosyl methionine onto catechol moieties, resulting in their deactivation.

- The COMT genetic variant rs4680 (val158met) is an extensively studied single nucleotide polymorphism (SNP) that encodes a valine-to-methionine substitution.

- This functional polymorphism results in the methionine variant having a 3- to 4-fold lower enzymatic activity than the valine variant.

- WGHS* participants had a 34% lower risk for the primary outcome (major CVD) with each additional valine allele in the COMT (val158met) SNP.

* WGHS: Women’s genome health study
Genetic variants of the Catechol-O-Methyltransferase Modify the Treatment Effect of Vitamin E on Cardiovascular Diseases (Kathryn T. Hall et al, 2014, Arterioscler Thromb Vasc Biol)

- Vitamin E (vs placebo) had a **47% risk reduction** for major CVD in the participants carrying the homozygous methionine allele of this COMT polymorphism.

- The authors conclude: ... the lack of an overall effect of vitamin E on CVD risk in the original WGHS* report **does not preclude** the possibility that subgroups defined on the basis of genetic strata experience benefit ...

- ...This may provide insights in the conflicting observations ... and overall null findings in CVD trials for vitamin E.

* WGHS: Women´s genome health study
Conclusions

- Today’s nutrition: One size does not fit all

- The anti-oxidative function of vitamin E is well established and is the basis on which the daily intake recommendations (which should be achieved by the diet) for vitamin E have been developed

- Emerging evidence supports the concept for a dual role of vitamin E in human health, which is at intakes / doses exceeding the RDA by a multiple

- Such ‘pharmacological’ benefits of vitamin E are conceivable (which can typically not been achieved by a diet) for
  - Diabetes
  - CVD pts
    - carrying a particular genotype

- Emerging science supporting a ‘dual role’ for vitamin E in human health is encouraging and further research is recommended to better understand the implications of nutrient gene interaction on human health