Vitamin E – new emerging data, the way forward

3rd World Congress of Public Health Nutrition
Las Palmas de Gran Canaria, Spain

DSM Satellite Symposium on 11th November 2014
17:00–19:00h at Conference Room: Gran Canaria
2012 celebrated the landmark of 100 years of vitamins. Vitamins play an essential role for health, wellness and disease prevention throughout the lifecycle. They are key to solving our global nutritional challenges. ‘Vitamins in Motion’ refers to this extraordinary landmark and builds on what has been achieved so far. It translates science and technological advances into nutritional solutions for health benefits worldwide. DSM takes the lead in these developments and is committed to making further scientific advancements for generations to come. DSM is proud of its role in setting vitamins in motion.


Bright Science, Brighter Living

Using groundbreaking science based on in-depth knowledge and understanding of customer and consumer needs, DSM creates innovative solutions and shares scientific expertise and leadership in the field of micronutrients. We care about the world’s populations in need of nutritional solutions, and exist to help improve their health status.
Vitamin E – new emerging data, the way forward

Foreword

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Manfred Eggersdorfer, University Groningen and DSM, Switzerland

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Keith West, Johns Hopkins School of Public Health, Baltimore

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Peter Weber, University Stuttgart and DSM, Switzerland

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Szabolcs Péter, DSM, Switzerland

Vitamin E in reduction of progression of Alzheimer disease page 20
Maurice W. Dysken, Minneapolis VA Health Care System

Panel discussion
It is widely accepted that the simplest way of receiving essential nutrition is through a healthy and varied diet. However, a large proportion of the population in the Western world is not adequately nourished. The intake of micronutrients, such as vitamin E, is vital for health. The objective of this symposium is to analyze the biological function of vitamin E as a powerful antioxidant and to discuss the current data on vitamin E status worldwide. Dietary recommendations are established in many countries around the world and refer to the essentiality of vitamin E and its important role in preserving the integrity of the cell membrane.

At the same time emerging data suggest that vitamin E in higher doses holds the promise for roles beyond essentiality for selected individuals and populations groups. For example, initial research shows for instance the overall finding that vitamin E may protect essential fatty acids from lipid peroxidation, and that improved vitamin E status is protective for cognitive function. High plasma levels of vitamin E have been associated with a reduced risk of Alzheimer’s disease.

Vitamin E supplementation may further reduce the negative health implications of fatty liver disease. The results of several clinical studies suggest that the use of vitamin E is associated with a number of benefits in patients with non-alcoholic liver disease. These findings may have major public health implications because this disorder is a consequence of overweight and obesity, which is a growing issue globally.

Looking at low income countries, the prevalence of vitamin E deficiency and its public health importance remain poorly characterized aspects of Hidden Hunger. This arising from assumed low prevalence, difficulty and of measurement, lack of evidence on consequence, and uncertainty about the roles of vitamin E in health. These are few examples showing that the issue of low vitamin E intake has to be widely addressed, because of its potential subclinical and clinical consequences. DSM is currently engaging with a number of experts in the field of vitamin E research to address the need for further studies into the micronutrient. Through communication of progressive research, the symposium will demonstrate that nutrition related solutions can play a vital role in tackling a number of global health concerns.

I look forward to your active participation in this meeting and in the realization of our goals.

Prof. Manfred Eggersdorfer
Vitamin E is essential for human health and achieving an optimal status is associated with beneficial health outcomes. Dietary recommendations are established in many countries around the world and refer to the important role of vitamin E in preserving the integrity of the cell membrane. The intake of vitamin E is in general low and very similar over all regions worldwide. Based on a search in the Pubmed/Medline database focused on population based studies published between January 1st 2000 and July 30th 2012 for a major part of the population intakes for α-tocopherol and vitamin E are below 15 mg /d, which is the Recommended Daily Allowance (RDA) for men and women in the US. Given the fact that people in many countries are not meeting vitamin E intake recommendations we assessed serum α-tocopherol. We used 12 µmol/L vitamin E serum levels needed to avoid deficiencies in the human body (F.a.N. Board 2000). Results from a number of observational, prospective studies suggest a serum tocopherol concentration of 30 µmol/L and above to have beneficial effects on human health in the field of cardiovascular disease and some cancers.

The data from the 2003-2006 National Health and Nutrition Examination Survey (NHANES) show mean α-tocopherol concentrations below the optimal concentration for the total population and non-supplements users. In addition to differences in α-tocopherol concentration between supplement and non-supplement users subpopulations by gender and race/ethnicity, a higher proportion of younger than older adults had suboptimal α-tocopherol concentrations. As a consequence, despite low incidence of overt vitamin E deficiency many American adults have suboptimal α-tocopherol status even when supplementing their diet. Data on vitamin E status worldwide will be discussed.

The issue of low vitamin E intake and serum level has to be widely addressed because of its potential subclinical and clinical consequences.
Vitamin E is essential
- Vitamin E is a powerful antioxidant. Once oxidized, it can be regenerated by vitamin C.
- Vitamin E depletion and repletion affects gene expression in vitro in cells and in vivo in animal models, which indicates broader effects.
- Incorporation of vitamin E into cellular membranes can alter the activity of membrane-associated proteins and thereby change signal transduction pathways.
- EFSA granted an Health Claim: “Vitamin E contributes to the protection of cells from oxidative stress.”

Do populations get an adequate intake of vitamin E via the diet?

Human daily vitamin E requirements are defined by IOM

<table>
<thead>
<tr>
<th></th>
<th>EAR Estimated Average Requirement</th>
<th>RDA Recommended Dietary Allowance</th>
<th>Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>12 mg</td>
<td>15 mg</td>
<td>1000 mg</td>
</tr>
</tbody>
</table>

Similar recommendations are established in other countries

Food and Nutrition Board, Institute of Medicine, Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids
http://www.nal.usda.gov

US: Most people do not consume the average required amount of vitamin E

Vitamin E intake is also low in other countries

Intake of vitamin E depends on diet

- Optimal diet rich in vegetables and fruits with sunflower oil
- Diet rich in vegetables and fruits with soybean oil
- Diet low in vegetables and fruits with soybean oil
- Diet low in vegetables and fruits with soybean oil older 60 days

Reference:
- Hsing et al. What we eat in America, NHANES 2007-2008
- http://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/micronutrients/vitamine_e.pdf
Low vitamin E stability may be a hidden factor for low intake

<table>
<thead>
<tr>
<th>Tocopherol isomer</th>
<th>decrease [1] day 28</th>
<th>day 56</th>
</tr>
</thead>
<tbody>
<tr>
<td>dark</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22°C</td>
<td>3.8 x 1.49</td>
<td>1.9 x 1.23</td>
</tr>
<tr>
<td>light</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22°C</td>
<td>3.3 x 1.35</td>
<td>1.9 x 1.35</td>
</tr>
</tbody>
</table>

- Unlacked stability of vitamin E in edible oils
- 60% of α-tocopherol disappears within 56 days
- May cause a low vitamin E status

What does this mean for the vitamin E intake?

Vitamin intake data are predominantly delivered by surveys

- Risk of under- and overreporting of food intake
- Surveys do not take actual bioavailability into account
- Comparability between surveys is often difficult due to differences in methodology
- Nutrient databases do not fully represent food options being consumed

Biomarkers are regarded as more accurate for dietary assessment. However if identified, scientific consensus generally accepted cut-offs are difficult to achieve.

Using NHANES data as source for vitamin E status in the US

- NHANES data 2003-2006 analyzed
- Vitamin E status differs by population groups
- Elderly have higher vitamin E levels compared to children and young people
- Analyses in other countries ongoing

Can we identify cut-off points for deficiency and optimal status?

Defining “deficiency” vitamin E status

- In vitro erythrocyte hemolysis during experimental human vitamin E deficiency
- IOA defined a status below 12 μmol/L as deficient
- Erythrocyte hemolysis

Defining “optimal” vitamin E status

A number of publications support benefits for vitamin E at or above 30 μmol/L serum concentration (prevention of CVD, different types of cancer, cognitive impairment)

This is further supported by the fact that α-CEHC excretion in urine increases at this level

Pentane concentration in exhaled air (marker for oxidative stress) is inversely related to vitamin E intakes and low at serum levels of 30 μmol/L

The Alpha-Tocopherol/beta-Carotene (ATBC) study shows a relationship between baseline vitamin E status and lowest total mortality at 30 μmol/L

Urinary α-CEHC may be used as a predictor of α-tocopherol adequacy

α-Tocopherol is metabolized to carboxy ethyl hydroxy chroman (α-CEHC)

Urinary α-CEHC excretion remains at a plateau (median, 1.39 μmol/g creatinine), until a level of α-tocopherol exceeds 30 μmol/L

Thus, a daily excretion of <1.99 μmol α-CEHC/g creatinine may be associated with adequate or optimal α-tocopherol status as evidenced by increased vitamin E metabolism and excretion.

In summary

- Intake of vitamin E depends on diet
- The intake of vitamin E is in general low and very similar over all regions; low stability of vitamin E in vegetable oils may be a hidden factor for it
- The data from the 2003-2006 National Health and Nutrition Examination Survey (NHANES) show especially for younger people mean co-tocopherol concentrations below the "optimal" level
- The issue of low vitamin E intake and serum level has to be widely addressed because of its potential subclinical and clinical consequences
- We need more research and new approaches to support optimal vitamin E status in populations
The prevalence of vitamin E deficiency and its public health importance remain poorly characterized aspects of Hidden Hunger in low income countries, arising from assumed low prevalence, difficulty and of measurement, lack of evidence on consequence and uncertainty about roles of vitamin E isomers in health. More research is needed to discern prevalence and health effects of vitamin E deficiency. We report here findings from two population studies in South Asia: a case-cohort study of 1st trimester vitamin E (α- and γ-tocopherol) status and risk of miscarriage in rural Bangladesh and a study among young school-aged children in Nepal to discover a plasma proteome associated with circulating concentrations of α- and γ-tocopherol that could stimulate use of protein biomarkers to assess vitamin E status using lower cost assays in the future.
Frontiers in Assessing Vitamin E Deficiency and its Public Health Consequence in South Asia

Keith P. West, Jr., D.PH. MPH. RD
Professor and Director
Center for Human Nutrition
Sight and Life Global Nutrition Research Institute
Department of International Health
Johns Hopkins Bloomberg School of Public Health
Baltimore, Maryland, USA

Vitamin E Frontiers in Low Income Countries

- Definition and assessment of vitamin E status and deficiency across vulnerable life stages
- Elucidation of adverse health conditions associated with vitamin E deficiency
  - Undernourished populations
  - Populations in transition
- Conduct of intervention trials to define the public health burden due to vitamin E deficiency and health benefits of repletion

Micronutrient Deficiencies Affect the World’s Poorest

Nutrient Deficiencies
- Vitamin A
- Iron
- Fat-soluble
- Iodine
- Zinc
- ...but also...
- Vitamin B, D, E, K
- B-complex
- Vitamin C
- Selenium
- Copper
- Others
- compounded by...
- Protein-energy deficit
- Inflammation/infection
- Abnormal micronutrient
- Environmental trauma

Child and Maternal Health Problems
- Infant or Child
- Infection
- Poor growth
- Impaired cognition
- Motor & behavioral development
- Mortality
- Mother
- Infection
- Pregnancy
- Fetal stress
- Obstetric problems
- Poor birth outcomes
- Morbidity

Chronic disease, disability, mortality

Both Sites Reflect Diet, Culture & Environment of Genetically South Asia

Multiple Micronutrient Deficiencies Affect Women during Pregnancy in Rural Nepal (NNIPS-3 Trial, Sauraha District)

Vitamin E Deficiency

Jiang T et al J Nutr 2005
Two Vitamin E Studies in South Asia

- **Bangladesh**: Case-cohort study of early antenatal vitamin E deficiency and risk of miscarriage in 1605 rural Bangladeshi pregnant women
- **Nepal**: Exploratory proteomics study in 500 young, rural school-aged children to identify and quantify a plasma α-tocopherol, that may reflect vitamin E status

### Case Cohort sub-Study of Pregnant Mothers in Bangladesh (JiVitA-1)

- Women visited during 5-weekly home surveillance
- Pregnancies detected by history of amenorrhea, verified by urine test
- Informed, consented, interviewed, measured, bled
  - Blood centrifuged, separated, shipped to INMU, Bangkok
  - HPLC analysis for retinol, carotenoids & tocopherols
- Began daily iron-folic acid or multiple micronutrient
- Followed for pregnancy outcomes: miscarriage, abortion stillbirth, live birth; infant & maternal survival

### First Trimester Vitamin E Deficiency and Risk of Miscarriage in Rural Bangladesh (JiVitA-1)

<table>
<thead>
<tr>
<th>Non-miscarriage, %</th>
<th>Miscarriage, %</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.2 (12.7, 32.0)</td>
<td>22.8 (18.2, 29.1)</td>
<td>0.98 (0.75, 1.28)</td>
</tr>
</tbody>
</table>

Model 1: adjusted for plasma concentration of other tocopherol & cholesterol
Model 2: additionally adjusted for maternal age, gravidity & GA at blood draw
Model 3: additionally adjusted for Apg


### Vitamin E Deficiency: Common in South Asia

- In Bangladesh,
  - Maternal α-tocopherol deficiency (<12 μmol/L) associated with 2x higher risk of miscarriage
  - Low maternal plasma γ-tocopherol concentrations associated with 40% lower risk of miscarriage
- Both associations were stronger in gravida with a
  - BMI >18.5 kg/m² (normal vs thin BMI)
  - Plasma ferritin >150 μg/L (normal vs high iron stores)
- Oxidative stress, critically regulated by vitamin E, may disrupt placenta during α-tocopherol deficiency
- Opposing influences of both tocopherols suggest an urgent area of research to understand influences of vitamin E isomers on reproductive health
Lecture by Keith P. West

Tapping the Plasma Proteome to Measure Vitamin E Status of Populations
Supported by Grant OPP5241 from the Bill and Melinda Gates Foundation

However, “Hidden Hunger” is just as hidden today as it was two decades ago

There is not a single developing country that has a current, nationally representative multiple micronutrient deficiency profile

Plasma Proteomics and Nutrients

- Several hundred proteins can be quantified in relative abundance in by tandem MS (iTRAQ)
- May enable discovery of proteins correlate with nutrient status (i.e., including vitamin E)
- By identifying proteins that covary with nutrients (via binding/complex networks), proteins can be modeled to estimate population nutrient status
- Strong prediction could allow population status for multiple micronutrients to be assessed by plasma proteomics in the future

Plasma Vitamin E Concentration* and Relative Abundance of Apo C-III (n=500)

* Log 2 scale

The Plasma Proteome Identifies Expected and Novel Proteins Correlated with Micronutrient Status in Undernourished Nepalese Children

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Progress to Date:
Plasma Nutriproteome for Micronutrient Assessment

- Initial predictive models (R^2=>0.60) available for vitamins A, E, K;
  - selenium, copper
  - acute phase proteins (CRP, AGP)
  - Holo-lipoproteins (HDL, LDL)
- Strong models (R^2=0.45-0.59) available for
  - vitamins D and B6, some carotenoids (beta-cryptoxanthin, lutein-zeaxanthin)
- Models not available for folate, vitamin B12

Funding Agencies:
Trials and Proteomics Studies

- The Bill and Melinda Gates Foundation
  - Grant OPP 5241 (Nutriproteomics Studies)
  - Grant OPP 614 (Field Trial and follow up studies)
- US Agency for International Development (Field Trial)
- Sight and Life Global Nutrition Research Institute
Professor Peter Weber received his Ph.D. in Nutritional Sciences from the University of Bonn, Germany and his M.D. from the University of Münster, Germany. He trained in internal medicine with a subspecialty in endocrinology at the University of Mainz, Germany. He is a Professor of Nutrition at the University of Stuttgart-Hohenheim. He has original research publications in the field of iodine deficiency, metabolic syndrome, vitamin K and a number of publications reviewing vitamin status of populations, the role of vitamins and polyunsaturated fatty acids in human health.

In 2004 he was appointed Corporate Scientist for Human Nutrition & Health in DSM Nutritional Products in Kaiseraugst, Switzerland which includes the responsibility for the DSM Corporate Research Program for Nutrition.

A dual role for vitamin E – essentiality and beyond

Dietary intake recommendations for vitamin E are established in many countries around the globe and refer to its important role in preserving the integrity of the cell membrane as a powerful chain-breaking antioxidant. In the US the Recommended Daily Allowance (RDA) for vitamin E is 15 mg α-tocopherol in adults for both men and women, a value derived from the amount needed to prevent peroxide-induced hemolysis in vitamin E deficient subjects. So, the essentiality of vitamin E is well established and the intake needed to meet the RDAs can be achieved by a prudent diet. On the other hand, emerging data suggest that in diabetics carrying the haptoglobin genotype Hp 2-2 a daily intake of 400 mg vitamin E reduced a composite cardiovascular endpoint (cardiovascular death, myocardial infarction or stroke) significantly. In addition, there is several studies reporting an improvement in fatty liver disease (NASH) by daily intakes of 400-800 mg vitamin E in both, children and adults. A recent study found a reduction of functional decline in Alzheimer Disease at an intake of 2000 mg of vitamin E per day confirming earlier findings. Currently, available evidence is limited for a possible function of vitamin E in human health beyond its role as an essential micronutrient. However, there is encouraging data for it which point to specific conditions and diseases at intakes which are likely not to be achieved by regular diet and which may be applicable for selected individuals and groups rather than for the general population.
Lecture by Peter Weber

A dual role for vitamin E: Essentaility and beyond

Peter Weber, PhD, MD
Professor of Nutrition
Corporate Scientist Human Nutrition & Health
DSM Nutritional Products, Kaiseraugst, Switzerland

Recommended vitamin 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’
- Differ between the countries!

Function of vitamin E as antioxidant is established

- Vitamin E is a powerful 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 (protection 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”

Current RDAs for vitamin E are based on markers of cell membrane integrity

1. Lysis of red blood cells
   - 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 umol/L was derived to prevent hemolysis
   - To achieve a serum level of 12 umol/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)

Current RDAs for vitamin E are based on markers of cell membrane integrity

2. PUFA Intake

Vitamin E requirements related to PUFA’s Intake

<table>
<thead>
<tr>
<th>PUFA</th>
<th>Estimated intake (g/ day)</th>
<th>Vit. E requirement mg/day*</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLA</td>
<td>29 - 30</td>
<td>1.2 - 2.7</td>
</tr>
<tr>
<td>Linoleic</td>
<td>11 - 17</td>
<td>4.4 - 10.1</td>
</tr>
<tr>
<td>Linolenic</td>
<td>1.1 - 2.6</td>
<td>0.7 - 2.3</td>
</tr>
<tr>
<td>Arachidonic</td>
<td>0.4 - 1.0</td>
<td>0.3 - 1.2</td>
</tr>
<tr>
<td>Other LC-PUFA (DHA, EPA)</td>
<td>0.1 - 0.5</td>
<td>0.11 - 0.83</td>
</tr>
</tbody>
</table>

* The estimation is based on a range of 0.4 to 0.6 mg of α-tocopherol per gram of linoleic acid intake for humans

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 maybe required for specific applications

A higher intake of nutrients beyond nutritional requirements may provide additional benefits in defined groups
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 (Hp2-2).
- Diabetic individuals with Hp2-2 have a marked increase in 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.

Vitamin E reduces risk for nonalcoholic fatty liver disease

- In 2016, more than 1.5 billion adults, 20 and older, were overweight worldwide.
- As a consequence, the risk for nonalcoholic liver disease is increasing.
- Currently, no therapeutic intervention is available.

Solutions: Steatohepatitis → Cirrhosis → Hepatocellular carcinoma

Supplementation with vitamin E (at a dose of 400 mg) was superior to placebo for the treatment of nonalcoholic steatohepatitis in adults without diabetes.

Vitamin E slows the progression of Alzheimer’s disease

- AD is a age-dependent progressive neurological disease, the leading cause of dementia and the fourth-leading cause of death in industrialized societies.
- Numbers of deaths due AD increased by 60% within 8 years.
- There is no pharmacological therapy available to causally prevent AD.

Supplementation with vitamin E (at a dose of 2000 IU) delays the pathologies.
- No severe adverse effect was associated with the vitamin E treatment.

Vitamin E: Concept to address requirements for general population and risk groups

- Specific health benefits at intake beyond RDA:
  - Diabetes with Hp2-2
  - Osteo and fatty liver
  - Cognitive function
  - Air pollution

Solutions:
- For specific applications
- Higher doses
- Multivitamins
- RDA range

Essential role in human health at RDA level:
- Global map of intake/status
- Communicate function and benefits

Nutrition needs must be adapted to the changing lifestyle and environment (only communicating guidelines is not enough).

Demonstrated benefits of Vitamin E go beyond essentiality

- Asthma
- Prostate cancer
- Age-related macular degeneration
- Fertility
- Asthma
- Vitamin E
- Alzheimer’s disease
- Diabetes / cardiopulmonary disease

Number of publications from general searches on PubMed with the indicated keywords (November 18, 2014).
Vitamin E in risk reduction for fatty liver disease

Vitamin E is an essential micronutrient, which is a powerful peroxyl radical scavenger particularly in the lipid bilayer of the cell membrane. The spectrum of non-alcoholic fatty liver disease (NAFLD) associated with metabolic determinants extends from hepatic steatosis through non-alcoholic steatohepatitis (NASH) to cirrhosis. NAFLD is frequently associated with obesity, dyslipidaemia, insulin resistance and type 2 diabetes mellitus (its prevalence can reach 76% in obese persons), but it also can be observed in 16% to 20% of normal weight individuals. Recent studies reported that vitamin E improves pathophysiological and histological status in NAFLD and NASH patients. As oxidative stress acts as a trigger to initiate cellular injury, leading to a chronic inflammatory response, vitamin E might act in NAFLD in different ways: As a chain-breaking, lipid-soluble antioxidant, quenching peroxyl radicals or as an anti-inflammatory compound, antagonizing the production of inflammatory mediators. There are also measurable differences in the profile of chemical processes involving metabolites (metabolomics) of subjects who are likely (vs. unlikely) to respond to vitamin E treatment for NASH and in those experiencing histologic improvement (vs. no improvement) on treatment. At present, there is no approved drug for the treatment of NASH. It has been shown that vitamin E administered at daily dose of 800 IU/day improves liver histology in non-diabetic adults with biopsy-proven NASH. Besides this therapeutic effect, there may be options in a preventative setting as well, which has to be further evaluated.
Studies on vitamin E and NAFLD (2)

Possible mechanisms of action of vitamin E

- Oxidative stress acts as a "second hit" to initiate cellular injury, leading to chronic inflammatory response.
- Vitamin E might act in NAFLD as follows:
  2. Anti-inflammatory compound, inhibiting the expression of inflammatory mediators and reducing peroxisomal proliferation.
  4. Other mechanisms include improving insulin sensitivity.

Vitamin E reduces risk for non-alcoholic fatty liver disease

- In 2010, more than 1.5 billion adults, 20 and older, were overweight worldwide.
- As a consequence, the risk for non-alcoholic liver disease is increasing.

Supplementation with vitamin E (at a dose of 400 mg) was superior to placebo for the treatment of nonalcoholic steatohepatitis in adults without diabetes.

Management of NAFLD and NASH

- At present, no approved drug for the treatment of NASH.
- Lifestyle intervention with diet and increased physical activity is the cornerstone of management in NAFLD/NASH.

Vitamin E (tocopherol) administered at daily dose of 800 IU/day improves liver histology in non-diabetic adults with biopsy-proven NASH. Further data supporting its effectiveness became available, vitamin E is not recommended to treat NASH in diabetic patients. NAFLD without liver biopsy, NASH chronic, or steatosis cirrhosis (Strehl-1, Quality - C).
Vitamin E in delaying the progression of Alzheimer disease

Alpha-tocopherol (vitamin E) has been studied in three large clinical trials to determine its benefit in patients with Alzheimer’s disease (AD) (Sano et al. 1997; Dysken et al. 2014) and in subjects with mild cognitive impairment (MCI) (Petersen et al. 2005). Sano et al. reported that 2000 IU/d of vitamin E delayed clinical progression by approximately seven months over a two year period in patients (N=341) with moderately severe AD. Dysken et al. reported that 2000 IU/d of vitamin E delayed clinical progression by approximately six months over two years in patients (N=613) with mild-to-moderate AD. Petersen et al. reported no benefit in delaying the progression of MCI to AD in subjects (N=769) with MCI. These three studies will be reviewed and discussed with emphasis on clinical trial methodology, mechanism of action, and implications for future research.
Vitamin E in delaying the progression of Alzheimer disease

Maurice W. Dysken, MD
Minneapolis VA Health Care System, Minneapolis, Minnesota

Alzheimer’s Disease

- First described by Alois Alzheimer, a German physician, in 1907
- Observed in a 53-year-old female patient with memory loss, disorientation, and hallucinations
- Postmortem studies characterized senile plaques and neurofibrillary tangles (NFTs) in the cerebral cortex
  - Senile plaques: Extracellular accumulation of insoluble fragments of beta-amyloid (Aβ)
  - NFTs: Intracellular accumulation of hyperphosphorylated tau strands

Mild Cognitive Impairment (MCI)

- Concern regarding a change in cognition
  - Patient or informant
- Impairment in one or more domains
  - Greater than expected for age and education
- Preservation in independence in functional abilities
- Not demented
- Conversion to Alzheimer’s disease (AD)
  - 12% to 15% per year

Current Pharmacological Treatments

- Alzheimer’s disease
  - Acetyl-cholinesterase inhibitors (AChEIs)
  - Memantine (Namenda)
  - Vitamin E
- Mild cognitive impairment
  - None
- Prevention
  - None

Alpha-tocopherol Clinical Trials in AD & MCI

- Sano et al. NEJM 1997
  - Vitamin E and selegiline in moderately severe Alzheimer’s disease (N=341)
- Petersen et al. 2005
  - Vitamin E and donepezil in mild cognitive impairment (N=769)
- Dysken et al. 2014
  - Vitamin E and memantine in mild-to-moderate Alzheimer’s disease (N=613)

Vitamin E and Selegiline: Delay in Clinical Progression of AD

Sano et al. NEJM 1997

Cumulative Survival (%)
Vitamin E and Memantine in Mild-to-Moderate Alzheimer’s Disease

- A Randomized Clinical Trial of Vitamin E and Memantine in Alzheimer’s Disease (CSP #546)
- To test the hypothesis that a combination of pharmacological therapies may be more effective in AD than individual treatments alone, CSP #546 examined the effectiveness of alpha-tocopherol (vitamin E) and memantine (Namenda) in mild-to-moderate AD patients already taking an AChEi

Primary Outcome – ADCS/ADL

- Mean Changes in Primary and Secondary Outcome Measures during the 4-year Study Period vs. Baseline

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vitamin E</th>
<th>Memantine</th>
<th>E + Memantine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s Disease Cooperative Study / Activity of Daily Living</td>
<td>N=140</td>
<td>N=142</td>
<td>N=139</td>
<td>N=140</td>
</tr>
<tr>
<td>Mean Annual Rate of Functional Decline</td>
<td>-7.64</td>
<td>-6.68</td>
<td>-6.45</td>
<td>-7.31</td>
</tr>
<tr>
<td>Least Square Mean Change (MCI)</td>
<td>-13.81 ± 1.11</td>
<td>-14.96 ± 1.10</td>
<td>-15.76 ± 1.11</td>
<td>-14.96 ± 1.11</td>
</tr>
<tr>
<td>Mean Difference Compared to Placebo (95% CI)</td>
<td>-3.13</td>
<td>1.98</td>
<td>1.76</td>
<td>-</td>
</tr>
<tr>
<td>p-Value</td>
<td>0.006</td>
<td>0.06</td>
<td>0.03</td>
<td>-</td>
</tr>
</tbody>
</table>

Secondary Outcomes – CAS

<table>
<thead>
<tr>
<th>Caregiver Activity Survey</th>
<th>N=140</th>
<th>N=142</th>
<th>N=139</th>
<th>N=140</th>
</tr>
</thead>
<tbody>
<tr>
<td>Least Square Means Change (MCI)</td>
<td>3.35 ± 0.78</td>
<td>5.52 ± 0.78</td>
<td>5.00 ± 0.78</td>
<td>5.14 ± 0.79</td>
</tr>
<tr>
<td>Mean Difference CI (%)</td>
<td>-1.79</td>
<td>0.31</td>
<td>-0.14</td>
<td>-</td>
</tr>
<tr>
<td>p-Value†</td>
<td>0.82</td>
<td>0.61</td>
<td>0.86</td>
<td>-</td>
</tr>
</tbody>
</table>

Conclusions

- Sano et al. NEJM 1997
  - Vitamin E delayed the clinical progression of moderately severe AD by about 7 months over two year follow-up
- Petersen et al. 2005
  - Vitamin E had no effect in slowing the rate of conversion from MCI to AD
- Dysken et al. 2014
  - Vitamin E delayed clinical progression of mild-to-moderate AD by 6.2 months over average length of study (2.3 years)